62. (Amended) The method of claim 60 wherein said integrin $\alpha_v\beta_5$ antagonist preferentially inhibits fibrinogen binding to $\alpha_v\beta_5$ compared to fibrinogen binding to $\alpha_{IIb}\beta_3$.

64. (Twice Amended) The method of claim 87 wherein said organic mimetic comprises the organic compounds selected from the group consisting of compounds 7, 9, 10, 12, and 14.

Please add new claims:

85. (new) The method of claim 60 wherein said antagonist is a polypeptide or a cyclic polypeptide.

86. (new) The method of claim 60 wherein said antagonist is a monoclonal antibody.

87. (new) The method of claim 60 wherein said antagonist is a organic mimetic compound.

REMARKS

Reconsideration of this application in view of the amendments above and the discussion below is respectfully requested.

Claims 49-59 and 63 are canceled. Dependent claims 85-87 have been added. Thus, claims 60, 61, 62, and 64-87 are pending. Claims 60, 61, 62 and 64 have been amended. Applicants have attached as Appendix II a copy of the currently pending claims as of this response. Appendix I provides the marked-up version of the amended claims.

Applicants believe that no new matter has been introduced by the amendments made herein.

I. The Amendments

Support for the amendments that do not add new matter to the noted claims is found in the specification and original claims. Support for amendment to claim 60 can be found at least in the title and at page 5, lines 13-19, wherein the distinct pathways of angiogenesis mediated by the different integrins, $\alpha_v\beta_5$ and $\alpha_v\beta_3$, is disclosed. The amendments were done to put the claims in condition for allowance and to promote administrative efficiency in view of priority as established for particular subject matter as further discussed in Section II below. The amendments do not require a new search or raise new rejections because they are responsive to issues already raised by the Examiner. Applicants respectfully request entry of the amendments. Applicants do not acquiesce to the grounds for rejection of the canceled claims to an article of manufacture, and reserve the right to pursue the subject matter in a later continuing application.

With regard to the comments, objections and rejections presented in the Action by the Examiner, Applicants' response continues below.

II. Priority and Related Amendment

The Examiner has requested that the specification be amended to recite prior applications and related priority information. The Examiner did not enter the information presented in the Application Data Statement (ADS) that was prepared in compliance with 37 CFR §1.76 and submitted with the last response mailed June 6, 2001. Applicants disagree with the Examiner's position that an ADS cannot be relied upon for a claim for priority. Applicants direct the Examiner's attention to 37 CFR §1.78(2) which specifically states the following as excerpted: "Except for a continued prosecution application filed under § 1.53(d), any nonprovisional application claiming

the benefit of one or more prior filed copending nonprovisional applications or international applications designating the United States of America must contain a reference to each such prior application, identifying it by application number . . . and indicating the relationship of the applications. **Unless the reference required by this paragraph is included in an application data sheet (§ 1.76)**, the specification must contain or be amended to contain such reference in the first sentence following any title." (Emphasis added). In accordance with the alternatives provided by the noted statutory provision, Applicants thus provided an acceptable ADS in the earlier response and argue that its submission is sufficient. However, Applicants have also provided the claim to priority in the specification to promote administrative efficiency. In view of the foregoing, Applicants request that the objections to the specification be withdrawn.

The Examiner has indicated that certain subject matter is entitled to particular priority dates. Applicants concur with that determinations with the following exceptions. The MMP-2 fragment identified as SEQ ID NO 17, is identified in the present specification on page 41, line 25, as "chMMP-2 (410-637)". In Provisional Application, 60/015,869, at page 3, lines 23-25, the same fragment is disclosed in the sentence beginning with "A GST fusion protein encoding amino acids 410-637 of the Gallus gallus (chicken) MMP-2, hereafter designated as CTMMP-2 (410-637),. . . " The fragment identified as SEQ ID NO 17 thus has support in the Provisional Application, 60/015,869, in contradiction to the Examiner's assertion that it is not supported. For the organic mimetics, the specification in the parent application, TSRI 481.0, filed August 14, 1995, discloses them broadly at least at page 33, line 23, and thus derives the benefit of August 14, 1995. The same is true for broadly disclosed monoclonal antibodies and peptides as being $\alpha_v\beta_5$ antagonists having support at least at page 33, lines 22 and 23. Peptides in the cyclic conformation are also disclosed in the TSRI 481.0 specification at least at page 42, line 28-29, with particular species of cyclic peptides described in the Examples. The species of

organic mimetics identified as compounds 7, 9, 10, 12, 14-18 are disclosed in the TSRI 481.1 specification, filed August 13, 1996. Applicants request reconsideration of the rejections of the pending claims, now amended, in view of the established claims for priority.

Applicants acknowledge the Examiner's withdrawal of a number of rejections in view of the valid priority claims.

III. Rejection under 35 U.S.C. §112, First Paragraph

Claims 49-57 and 59-84 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with it is most nearly connected, to make and/or use the invention.

The Examiner contends that claims 49, 51-53, 59, 60, 62 and 65-84 encompass claimed subject matter that is supported by an insufficient disclosure not enabling of one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. The Examiner's arguments are only directed to the lack of enablement of the $\alpha_v\beta_5$ antagonists as compositions and did not address them in the scope of the originally pending claims, namely an article of manufacture with specific instructions for use and a method of inhibiting angiogenesis with an $\alpha_v\beta_5$ antagonist.

Thus, Applicants argue that the Examiner has not met the requisite burden of providing evidence or reasoning to support the assertion of lack of enablement commensurate with the scope of the actual rejected claims. This argument applies despite the cancellation of the article of manufacture claims, the cancellation of which is without prejudice and acquiescence to the pending rejection. Applicants reserve the right to pursue the canceled subject matter in a continuing application.

Applicants further respectfully argue that the Examiner's assertion that "the specification discloses many inhibitors but fails to provide any specific guidance or

direction for making all the possible inhibitors or for selecting the particular inhibitor to use in treating the diseased tissues claimed." is without substantiation.

In traversing this rejection, Applicants direct the Examiner's attention to the specification where antagonists of $\alpha_v\beta_5$ are broadly as well as specifically described with respect to structural and functional characteristics, such enablement beginning at page 23, continuing to page 34. In particular, Applicants cite to Example 6 as exemplary teachings of the enablement of a number of $\alpha_v\beta_5$ antagonists including cyclic peptides, antibodies and MMP-2 fragments in functioning to significantly inhibit angiogenesis in a number of different experimental models. In addition, the specification in Example 7 teaches how to identify and screen an $\alpha_v\beta_5$ antagonist that is useful in the present invention. Thus, although the Examiner argues that the claimed subject matter poses the problem of unpredictability, Applicants contend that the number of $\alpha_v\beta_5$ antagonists in view of their different structure provides the requisite measure of predictability.

Enablement requires that the specification must teach how to make and use the claimed invention. The relevant inquiry in determining whether a particular claim is supported by the specification is whether the specification contains sufficient teachings **regarding the subject matter of the claim** as to enable one skilled in the art to make and use the invention. *In re Moore*, 169 USPQ 236, 239 (CCPA 1971; emphasis added). Second, enablement is not precluded even if some experimentation is necessary. *Atlas Powder Co. v. E. I. duPont de Nemours & Co.*, 224 USPQ 409, 413 (Fed. Cir. 1984). Although Applicants agree that the scope of enablement varies inversely with the degree of unpredictability of the technology involved, Applicants argue that they are not required to disclose every species encompassed by the claims. *In re Fisher*, 166 USPQ 18 (CCPA 1970). Applicants submit that "what the Patent Office is here attempting is to limit the claims to the specific examples, notwithstanding the disclosure of a broader invention. This it may not do." *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973).

Applicants thus assert that the specification teaches how to make and use an $\alpha_v\beta_5$ antagonist having the claimed characteristics and that one of ordinary skill in the art would have known how to practice the claimed invention without undue experimentation. In view of the foregoing, the teachings in the specification of how to make and use the claimed invention, Applicants assert that they are entitled to claims commensurate in scope with the teaching in the specification.

For the above reasons, Applicants submit that the rejections have been overcome to the remaining pending claims to the methods of inhibiting angiogenesis with an $\alpha_v\beta_5$ antagonist. As such, Applicants respectfully request that the rejections be withdrawn and the claims pass on to allowance.

IV. Rejection under 35 U.S.C. §103(a)

1. Claims 49 and 51-53

Claims 49 and 51-53 are rejected under 35 U.S.C. §103(a) as being unpatentable over Friedlander et al. This rejection is respectfully traversed.

The Examiner contends that the present invention is obvious in view of Friedlander et al. reference in allegedly describing $\alpha_v\beta_5$ antagonists and angiogenesis although it lacks any teaching or suggestion of an article of manufacture. Applicants contend that Friedlander et al. disclose the seminal basic research findings of the role of $\alpha_v\beta_5$ receptors in mediating angiogenesis and inhibition thereof with $\alpha_v\beta_5$ antagonists. Friedlander et al. do not disclose the requisite pharmaceutical formulations, do not disclose the dosages related to particular indications that are necessitated in an article of manufacture, and do not suggest an article of manufacture. A *prima facie* obviousness rejection cannot stand if the cited art does not suggest or motivate one to modify the art to reach the claimed invention. "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." *In re Gordon*, 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed.

Cir. 1984). The suggestion or motivation must be in the art and not cannot derive from the Applicant's specification in hindsight. Applicant's argue that the cited reference does not provide any basis for arriving at the present invention of an article of manufacture as a whole.

Therefore, in view of the foregoing, Applicants contend that the rejection for obviousness of the rejected claims is negated. The rejection is no longer applicable, however, in view of the cancellation of claims 49, and 51-53. Applicants thus respectfully request that the rejection for obviousness be withdrawn.

2. Claims 49 and 50

Claims 49 and 50 are rejected under 35 U.S.C. §103(a) as being unpatentable over Collier et al. and Chen et al. This rejection is respectfully traversed.

The Examiner alleges that the disclosure of the complete nucleotide and encoded amino acid sequences in both Collier et al. and Chen et al. render the present invention *prima facie* obvious regardless of the claimed article of manufacture.

Before the PTO can combine the disclosures of two or more prior art references to render the instant claims obvious, the prior art must contain some suggestion for doing so. *In re Fine*, 837 F.2D 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). Moreover, the court has recently ruled that the motivating suggestion must be explicit. *Winner International Royalty Corp. v Wang*, No 96-2107, 48 USPQ2d 1139 (D.C.D.C. 1998). In the present rejection, no such explicit motivation can even be manufactured from the teachings of either Collier et al. or Chen et al. that both do not describe any polypeptide fragments of the enzymes useful as $\alpha_v\beta_5$ antagonists in inhibiting angiogenesis. In addition, the cited references do not disclose the requisite pharmaceutical formulations, do not disclose the dosages related to particular indications that are necessitated in an article of

manufacture, and do not suggest an article of manufacture. Neither reference provides any teaching, suggestion or motivation, explicit or vague, of an $\alpha_v\beta_5$ antagonist of any species as a pharmaceutical and for use in an article of manufacture. One of ordinary skill in the art would not be motivated by the teachings of either Collier et al. or Chen et al. to arrive at the present invention as a whole for the purposes stated by the Examiner.

Therefore, in view of the foregoing, Applicants contend that the rejection for obviousness of the rejected claims is overcome. The rejection is no longer applicable, however, in view of the cancellation of claims 49 and 50. Applicants thus respectfully request that the rejection for obviousness be withdrawn.

3. Claims 49, 60, 62, 65, 66, 71-73, 75, 78 and 79

Claims 49, 60, 62, 65, 66, 71-73, 75, 78 and 79 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent Number 5,981,478 (filed August 4, 1994). This rejection is respectfully traversed.

The Examiner alleges that the cited patent teaches a pharmaceutical agent that can be an angiogenesis-inhibiting amount of an $\alpha_v\beta_5$ antagonist that is useful for inhibiting angiogenesis in a tissue. The Examiner cites to column 10, line 45 continuing to column 11, line 36, column 20 and claims 5, 19, 26 and 27. At these cited disclosures, there is no teaching or suggestion of angiogenesis being mediated by $\alpha_v\beta_5$, a pathway distinct in tissues and function from that of $\alpha_v\beta_3$. In addition, the patent lacks any teaching or suggestion of the use of an $\alpha_v\beta_5$ antagonist to inhibit $\alpha_v\beta_5$-mediated angiogenesis. In particular, at column 2, lines 51 -54, states that ". . . therapeutic methods useful for inhibiting angiogenesis also involve administering to an individual a peptide of the invention that binds to the $\alpha_v\beta_3$ integrin." (Emphasis added). Further disclosure limiting the patent to integrins other than $\alpha_v\beta_5$ involved in angiogenesis can be found at column 10, lines 34 and 35, stating "In particular, the method is directed toward tumors expressing $\alpha_5\beta_1$ and/or $\alpha_v\beta_3$ integrins. Lastly,

the patent lacks any teaching or suggestion that angiogenesis was in fact inhibited by any of the claimed peptides; the specification merely discloses activity of particular peptides in cell and receptor binding assays not in any models of angiogenesis.

Therefore, in view of the foregoing, Applicants contend that the Examiner has not met the burden for establishing a *prima facie* obvious rejection of the presently claimed invention as a whole for either the article of manufacture, now canceled as previously discussed, or for the method of inhibiting angiogenesis as disclosed in the present invention as a whole. As such, Applicants thus respectfully request that the rejection for obviousness be withdrawn and the pending claims pass on to allowance.

4. Claim 74

Claim 74 is rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent Number 5,981,478 (filed August 4, 1994), in view of U.S. Patent Number 5,567,693 (October 22, 1996). This rejection is respectfully traversed.

The Examiner contends that the present invention is obvious in view of U.S. Patent Number 5,981,478 for disclosing methods of inhibiting angiogenesis and combined with the teachings in the cited patent to administering chemotherapeutic agents. As discussed above, the U.S. Patent Number 5,981,478 lacks any explicit teachings or suggestions of the present invention. To establish a *prima facie* obvious rejection, the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the claimed invention. Applicants argue that the requisite burden of making a *prima facie* rejection is not met here as the U.S. Patent Number 5,981,478 lacks any teaching or suggestion of any $\alpha_v\beta_5$ antagonist useful for inhibiting angiogenesis and in particular angiogenesis mediated by the $\alpha_v\beta_5$ integrin.

Therefore, in view of the foregoing, Applicants contend that the rejection for obviousness of the rejected claim is negated. Applicants thus respectfully request that the rejection for obviousness be withdrawn and the claim pass on to allowance.

5. Claims 60, 76 and 77

Claims 60, 76 and 77 are rejected under 35 U.S.C. §103(a) as being unpatentable over Friedlander et al. (sic) over U.S. Patent 5,981,478. This rejection is respectfully traversed.

In this rejection, Applicant assumes that the Examiner meant to reject the noted claims over U.S. Patent 5,981,478 and not Friedlander et al. as the Examiner's arguments seem to be based on the patent and not on the teachings in Friedlander et al. Applicants' arguments are thus directed to the patent.

The Examiner argues that the cited patent teaches a method for inhibiting angiogenesis but does not teach the method where different routes of administration are contemplated as specified in claims 76 and 77.

For the foregoing bases argued in Number 3 and 4 above and further incorporated herein applicable to the present rejection, Applicants contend that the Examiner has not established a *prima facie* case of obviousness.

Therefore, in view of the foregoing, Applicants contend that the rejection for obviousness of the rejected claims is negated. Applicants thus respectfully request that the rejection for obviousness be withdrawn and the claims pass on to allowance.

V. Summary

Applicants believe that a complete response is provided in the foregoing amendments and remarks to each issue and grounds for rejection and objection raised by the Examiner. Applicants submit that patentable subject matter exists with regard to the pending claims and therefore respectfully request favorable action and entry of the presents Amendments and Response. The application is now believed

to be in proper condition for allowance and early notification of allowance is earnestly solicited. The Examiner is invited to telephone the undersigned if it would be deemed helpful to advance the application.

Respectfully submitted,

April 19, 2002
Date

Emily Holmes, Reg. No. 40,652

THE SCRIPPS RESEARCH INSTITUTE
Office of Patent Counsel
10550 North Torrey Pines Road
Mail Drop TPC-8
La Jolla, California 92037
(858) 784-2937

P:\Emily\WP\OA\MER0065P.rs2